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Abstract: BACKGROUND AND PURPOSE: Demographic changes will result in a rapid increase of patients age 90 years (nonagenarians), but little is known about outcomes in these patients after intravenous thrombolysis (IVT) for acute ischemic stroke. We aimed to assess safety and functional outcome in nonagenarians treated with IVT and to compare the outcomes with those of patients age 80 to 89 years (octogenarians). METHODS: We analyzed prospectively collected data of 284 consecutive stroke patients age 80 years treated with IVT in 7 Swiss stroke units. Presenting characteristics, favorable outcome (modified Rankin scale [mRS] 0 or 1), mortality at 3 months, and symptomatic intracranial hemorrhage (SICH) using the National Institute of Neurological Disorders and Stroke (NINDS) and Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria were compared between nonagenarians and octogenarians. RESULTS: As compared with octogenarians (n=238; mean age, 83 years), nonagenarians (n=46; mean age, 92 years) were more often women (70% versus 54%; P=0.046) and had lower systolic blood pressure (161 mm Hg versus 172 mm Hg; P=0.035). Patients age 90 years less often had a favorable outcome and had a higher incidence of mortality than did patients age 80 to 89 years (14.3% versus 30.2%; P=0.034; and 45.2% versus 22.1%; P=0.002; respectively), while more nonagenarians than octogenarians experienced a SICH (SICH(NINDS), 13.3% versus 5.9%; P=0.106; SICH(SITS-MOST), 13.3% versus 4.7%; P=0.037). Multivariate adjustment identified age 90 years as an independent predictor of mortality (P=0.017). CONCLUSIONS: Our study suggests less favorable outcomes in nonagenarians as compared with octogenarians after IVT for ischemic stroke, and it demands a careful selection for treatment, unless randomized controlled trials yield more evidence for IVT in very old stroke patients.

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Intravenous Thrombolysis in Nonagenarians with Ischemic Stroke

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Background and Purpose. Demographic changes will result in rapid growth of patients ≥ 90 years (nonagenarians), but little is known about outcomes in these patients after intravenous thrombolysis (IVT) for acute ischemic stroke. We aimed to assess safety and functional outcome in nonagenarians treated with IVT and to compare the outcomes with patients aged 80 to 89 years (octogenarians).

Methods. We analyzed prospectively collected data of 284 consecutive stroke patients ≥ 80 years treated with IVT in seven Swiss stroke units. Presenting characteristics, favorable outcome (modified Rankin scale 0 or 1), mortality at 3 months and symptomatic intracranial hemorrhage (SICH) using the NINDS and SITS-MOST criteria were compared between nonagenarians and octogenarians.

Results. As compared with octogenarians ($n=238$, mean age 83 years), nonagenarians ($n=46$, mean age 92 years) were more often women (70% vs. 54%, $p=0.046$) and had lower systolic blood pressure (161 mm Hg vs. 172 mm Hg, $p=0.035$). Patients ≥ 90 years had less often a favorable outcome and a higher incidence of mortality than patients aged 80 to 89 years (14.3% vs. 30.2%, $p=0.034$ and 45.2% vs. 22.1%, $p=0.002$, respectively), while more nonagenarians than octogenarians experienced a SICH (SICH_{NINDS} 13.3% vs. 5.9%, $p=0.106$; SICH_{SITS-MOST} 13.3% vs. 4.7%, $p=0.037$). Multivariable adjustment identified age ≥ 90 years as an independent predictor of mortality ($p=0.017$).

Conclusion. Our study suggests less favorable outcomes in nonagenarians as compared with octogenarians after IVT for ischemic stroke and demands a careful selection for treatment, unless randomized controlled trials yield more evidence for IVT in very old stroke patients.

1 INTRODUCTION

2 Age is the most important nonmodifiable risk factor for stroke and a major predictor of
3 clinical outcome after ischemic stroke, with increased mortality and higher risk of
4 intracranial hemorrhage by advancing age.¹⁻² In the elderly patients, evidence from
5 randomized controlled trials for benefit of intravenous thrombolysis (IVT) with alteplase
6 is scarce, as patients over 80 years of age were either underrepresented or excluded in
7 these trials.³⁻⁴ Several observational studies reported on outcomes in patients ≥ 80
8 years with ischemic stroke and suggested a potential benefit of IVT,⁵⁻⁷ but little is
9 known about outcome specifically in nonagenarians. Nonetheless, demographic
10 changes result in excessive growing of the “oldest-old” population. Thus, the number of
11 nonagenarians will increase almost eight-fold to 57 million by 2050 worldwide.⁸ We
12 therefore undertook this study to assess the rates of symptomatic intracranial
13 hemorrhage (SICH), mortality and favorable outcome in nonagenarians treated with
14 IVT for ischemic stroke and compared the data with outcomes in octogenarians.

PATIENTS AND METHODS

As a joint initiative of seven stroke centers in Switzerland, we designed a study to compare the outcome in nonagenarians with octogenarians after IVT for ischemic stroke. All participating centers used IVT according to current guidelines.⁹ Neither center applied an upper age limit for IVT, because in Switzerland alteplase is licensed for ischemic stroke without age restrictions.⁷ Patients and relatives were informed about limited evidence for the effectiveness of alteplase in patients aged ≥ 80 years, however, and informed consent was obtained prior to treatment. A standardized form was used to collect data with pre-defined variables as it was also done in a previous study with similar methodology.¹⁰ We analyzed data of consecutive patients aged 80 years or older who were treated with intravenous alteplase for acute ischemic stroke between January 1, 2000, and December 31, 2008.

The following variables were ascertained: age, gender, vascular risk factors according to pre-defined criteria,¹⁰ history of coronary artery disease, antithrombotic medication at stroke onset, baseline National Institutes of Health Stroke Scale (NIHSS) score, stroke etiology according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST)-criteria, time to treatment, blood pressure and blood glucose level obtained at admission. All patients treated with IVT were admitted to intermediate or intensive care units for at least 24 hours. All patients underwent brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) 24 to 48 hours after IVT and in any case of clinical deterioration. Clinical outcome was assessed by outpatient visits or structured telephone interviews using the modified Rankin Scale (mRS) score at 3 months.

The primary outcome measures were favorable outcome, defined as mRS score 0-1 and mortality at 3 months. Secondary, we assessed the rate of SICH by applying the definition from the National Institute of Neurological Disorders and Stroke trial

(SICH_{NINDS}).³ In addition, we also used the more conservative definition from the the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SICH_{SITS-MOST}).¹¹

Statistical analysis

Normally distributed data were expressed as mean±standard deviation (SD) and compared using unpaired, two-tailed t-test. The two groups (nonagenarians and octogenarians) were compared using Mann Whitney *U* test for continuous variables and a chi-square or a Fisher's exact test (the latter if some expected counts in the two-by-two table were less than 5) for binary variables. Multiple logistic regression analyses were performed to assess the joint effects of age and stroke risk factors on the outcome parameters SICH, mortality and favorable outcome. In a first step, the influence of every single potential predictor on the outcomes was evaluated using univariate logistic regression analyses. The parameters examined were baseline NIHSS score, time to treatment, systolic and diastolic blood pressure, blood glucose level on admission (continuous variables), age (80 to 89 years vs. 90 to 99 years) patients gender, arterial hypertension, smoking, diabetes mellitus, hypercholesterolemia, coronary heart disease and antithrombotic medication with antiplatelets or anticoagulants at stroke onset (categorical variables). In a second step, a multivariate logistic regression analysis was performed, including all potential predictors with a p-value <0.2 from univariate analyses into the model. Significance was declared at p<0.05 level.

RESULTS

Forty-six nonagenarians (mean age 92, range 90 to 99 years) and 238 octogenarians (mean age 83, range 80 to 89 years) were eligible for this study. As compared with their counterparts, nonagenarians were more often women (70% vs. 54%, $p=0.046$), had a lower systolic blood pressure (160 mm Hg vs. 172 mm Hg, $p=0.035$) and tended to have slightly more severe strokes by a mean NIHSS score of 1.5 points, which was not significant however (Table 1). Nine of 46 (19.6%) nonagenarians and 52 of 238 (21.8%) octogenarians were treated beyond the 3-hour time window ($p=0.730$), while ten of 237 (4.2%) octogenarians and none of nonagenarians were treated with oral anticoagulants at stroke onset ($p=0.375$). Time to treatment and other vascular risk factors did not differ significantly between the two groups (Table 1).

At three months, six of 42 nonagenarians reached a favorable outcome (Table 2). In comparison, the frequency of favorable outcome in octogenarians was significantly higher (30.2% vs. 14.3%, $p=0.034$). Logistic regression analyses identified NIHSS score ($p<0.001$), antiplatelet medication ($p=0.003$), diabetes mellitus ($p=0.006$) and anticoagulants ($p=0.007$) to be independently associated with clinical outcome at three months, while the association with age ≥ 90 years was no longer significant ($p=0.147$). Within the nonagenarian group, six out of 10 (60%; 95% CI 23.1-96.9) men experienced a favorable outcome, whereas all 32 (100%) women had an unfavorable outcome ($p<0.001$). Furthermore, nonagenarians with a favorable outcome had less severe strokes (mean NIHSS score 11 vs. 16 points, $p=0.028$), whereas no association was identified with time to treatment and the age of nonagenarians. Mortality in nonagenarians was significantly higher as compared with octogenarians (45.2% vs. 22.1%, $p=0.002$) (Table 2). After multivariable adjustment, independent predictors of mortality were age ≥ 90 years ($p=0.017$), anticoagulants ($p=0.049$) and the NIHSS score ($p<0.001$).

1 Classification of SlCH was available in 45 of 46 nonagenarians. Six patients aged
2 ≥90 years experienced a SlCH (according to NINDS and SITS-MOST criteria), five of
3 them were fatal and one caused severe disability (mRS 5). Compared with
4 octogenarians, the risk of SlCH in nonagenarians was about two-fold higher. The
5 difference was statistically significant by using the SITS-MOST criteria (13.3% vs.
6 4.7%, $p=0.037$), but not the NINDS criteria (13.3% vs. 5.9%, $p=0.106$) (Table 2).
7 Multivariate analyses did not identify an independent predictor of SlCH. In
8 nonagenarians, 5 of 6 (83.3%) SlCH were fatal. In comparison, 5 of 14 (35.7%) SlCH
9 were fatal in octogenarians, but the difference was statistically not significant ($p=0.141$).
10 Fatal SlCH in nonagenarians (5/19, 26.3%) tended to account more often for mortality
11 as compared with octogenarians (5/52, 9.6%). The difference was statistically not
12 significant ($p=0.118$).

13

DISCUSSION

This multicenter observational study assessed clinical outcomes in stroke patients ≥ 90 years treated with IVT and suggests poor outcomes for this age group: about one out of seven patients reached a favorable outcome and nearly half of the population died within the first three months after stroke, while 13% of patients experienced a SICH, all of them causing either death or severe disability. Nonagenarians had an about two-fold higher risk for unfavorable outcome, mortality and SICH as compared with octogenarians.

Only 6 of 42 (14%) nonagenarians reached a favorable outcome at three months, while clinical outcome was favorable in 30% of octogenarians ($p=0.034$). Our results are in concordance with the study from Mayo Clinics that reported favorable outcome in 2 of 20 (10%) alteplase treated nonagenarians at 30 days.¹² In contrast, the recently published post-hoc analysis of the Canadian Activase for Stroke Effectiveness Study (CASES) showed similar outcomes in nonagenarians at 30 days as compared with octogenarians (30% vs. 26%).¹³ In our population of nonagenarians, age, stroke severity and time to treatment were similar to those observed in the CASES registry and thus do not explain the different outcomes. Comorbidities (e.g. previous stroke, cancer, dementia, congestive heart failure) and pre-stroke disability might have differed between the two populations as a probable explanation. Another finding of our study is the worse clinical outcome in women ≥ 90 years as compared to their male counterparts. This may have implications for clinical practice, since women comprise higher population proportions in advanced age and the female-male ratio will dramatically increase by every decade of age in future.⁸ However, the wide 95% CI preclude any definite conclusion.

The 3-month mortality in nonagenarians treated with IVT reached 45%, which was two-fold higher as compared with octogenarians. Our finding is in concordance with

1 three recent studies that reported a 3-month mortality of 51% to 59% in stroke patients
2 ≥ 90 years undergoing IVT.¹²⁻¹⁴ The higher incidence of SICH in nonagenarians may
3 have contributed to the difference in mortality between the two populations.
4 Furthermore, age is an independent predictor of mortality and studies on IVT reported
5 an increased 3-month mortality with older age up to 40 % in stroke patients ≥ 80
6 years.¹⁵ The same is true for elderly stroke patients who are not treated with IVT.¹⁶ The
7 3-month mortality of 45% reported in stroke patients ≥ 80 years without thrombolysis is
8 consistent with that observed in nonagenarians from our study.¹⁷ Finally, mean NIHSS
9 score in nonagenarians was by 1.5 points higher than in octogenarians and multivariate
10 analyses identified NIHSS score as an independent predictor of mortality. These data
11 suggest that, rather than IVT alone, other factors such as older age, comorbid
12 conditions and stroke severity may have been substantially related to the high mortality
13 in nonagenarians which was consistent with the natural history reported in this age
14 group.

15 The rate of SICH in nonagenarians was higher as compared with octogenarians,
16 and the difference was significant according to the SITS-MOST criteria, but not
17 according to the NINDS criteria. Age ≥ 90 years did not predict SICH after multivariate
18 logistic regression analyses, but all SICH in this age category were severe, and most of
19 them leading to death. In comparison, data from CASES registry showed a relative risk
20 of 1.7 for SICH in nonagenarians as compared with octogenarians after IVT, which was
21 not statistically significant. The higher incidence of SICH in patients ≥ 90 years may be
22 explained by impaired ability to clear alteplase and higher frequency of cerebral
23 amyloid angiopathy and leukoaraiosis by advancing age, that might be more
24 pronounced in nonagenarians than in octogenarians. In contrast, the risk of SICH in
25 octogenarians was comparable to that of the NINDS trial and is line with the findings of

1 a systematic review and a recently published large-scale study that reported a similar
2 risk of SICH in stroke patients aged ≥ 80 and < 80 years of age.^{14, 18}

3 This study has some limitations. It is a multi-center, observational study performed in
4 clinical setting, and IVT was performed at the discretion of the treating physicians.

5 Thus, a selection bias is likely and baseline characteristics such as age, stroke severity,
6 blood pressure, glycemia and imaging findings might have influenced the decision
7 whether to administer IVT or not. Some baseline variables that could potentially
8 influence stroke outcome such as previous stroke in past medical history, pre-stroke
9 disability and atrial fibrillation were not available for analysis. Furthermore, the cohort
10 size of nonagenarians was small, the possibility of a type 2 error must be admitted.
11 Finally, there is no age-matched control group and the assessment of the mRS score at
12 3 months was not blinded to the clinical condition of the patients during the hospital
13 stay and at discharge.

14 In conclusion, the observational design of this study does not allow us to judge the
15 efficacy and safety of IVT in nonagenarians with ischemic stroke. Nonetheless, our
16 data suggest less frequent favorable outcomes, higher mortality and more frequent
17 SICH in nonagenarians as compared with octogenarians. These findings may be useful
18 for accurate adjusting of patient and family expectations. Furthermore, a careful
19 selection of patients ≥ 90 years for IVT is needed in view of less favorable outcomes in
20 this age population. Randomized controlled trials such as the ongoing International
21 Stroke Trial (IST)-3 would yield more evidence on the balance of risk and benefit of IVT
22 in stroke patients aged 90 years and older,¹⁹ whereas our study could hopefully
23 stimulate further research interest in this progressively growing very old patients
24 population.

Table 1. Baseline Characteristics of Nonagenarians and Octagenarians Treated with Intravenous Thrombolysis

	Nonagenarians (n=46)	Octagenarians (n=238)	P Value
Male sex [%]	14/46 (30.4)	110/237 (46.4)	0.046
Hypertension [%]	39/46 (84.8)	193/238 (81.1)	0.554
Current smoking [%]	3/45 (6.7)	29/238 (12.2)	0.284
Diabetes mellitus [%]	5/45 (11.1)	33/238 (13.9)	0.619
Hypercholesterolemia [%]	12/44 (27.3)	93/235 (39.6)	0.122
Antiplatelet medication at stroke onset [%]	24/46 (52.2)	107/237 (45.1)	0.382
Anticoagulation at stroke onset [%]	0/46 (0)	10/237 (4.2)	0.375 [†]
Coronary artery disease [%]	13/45 (28.9)	50/238 (21.0)	0.244
Mean NIHSS score ± SD	14.4 ± 6.7	12.9 ± 5.9	0.126*
Time to treatment ± SD	148.8 ± 51.1	159.6 ± 40.7	0.116*
Mean systolic blood pressure ± SD [mm Hg]	161.1 ± 28.7	172.0 ± 25.9	0.035*
Mean diastolic blood pressure ± SD [mm Hg]	85.7 ± 20.8	90.1 ± 18.0	0.175*
Mean blood glucose ± SD [mmol/L]	7.0 ± 2.9	7.1 ± 2.3	0.842*
Cause of stroke			
Large artery atherosclerosis [%]	10/45 (22.2)	79/238 (33.2)	
Cardiac embolism [%]	22/45 (48.9)	80/238 (33.6)	
Small artery disease [%]	2/45 (4.4)	13/238 (5.5)	0.312
Other determined etiology [%]	0/45 (0)	4/238 (1.7)	
Undetermined etiology [%]	11/45 (24.4)	62/238 (26.1)	

NIHSS denotes National Institutes of Stroke Scale, IVT intravenous thrombolysis, and SD standard deviation

P-values apply to chi-square tests unless otherwise indicated

* t-test, [†] Fisher exact test

Table 2. Favorable Outcome, Mortality and Symptomatic Intracranial Hemorrhage in Nonagenarians and Octogenarians Treated With Intravenous Thrombolysis

	Nonagenarians n/N, % (95% CI)	Octogenarians n/N, % (95% CI)	P Value Univariate	P Value Logistic Regression
Favorable Outcome	6/42 14.3 (3.2-25.3)	71/235 30.2 (24.3-36.1)	0.034	0.130
Mortality	19/42 45.2 (29.5-60.9)	52/235 22.1 (16.8-27.5)	0.002	0.017
Symptomatic ICH				
per NINDS	6/45 13.3 (3.0-23.7)	14/236 5.9 (2.9-9.0)	0.106*	0.130
per SITS-MOST	6/45 13.3 (3.0-23.7)	11/236 4.7 (2.0-7.4)	0.037*	0.138

ICH denotes intracranial hemorrhage, NINDS National Institute of Neurological Disorders and Stroke, SITS-MOST Safe Implementation of Thrombolysis in Stroke-Monitoring Study

P-values apply to chi-square tests unless otherwise indicated

* Fisher exact test

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